Mortality From Congenital Cardiovascular Malformations in Japan, 1968 Through 1997

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Long-term mortality from congenital cardiovascular malformations (CCVM) remains unknown in most countries. Age- and sex-specific mortality rates from CCVM in Japan from 1968 through 1997 were determined from analyses, with official permission, of individual death records held by the Japanese Government. CCVM with chromosomal anomalies were not included. The number of deaths analyzed was 82,919. The mortality rate declined by 64% from 3.36 per 100,000 population in 1968 to 1.22 in 1997, largely because of a decrease in mortality among patients under 20 years of age. Infant mortality remained high until 1978, then sharply declined from 1979 to 1987 with the advent of 2-dimensional echocardiographic diagnosis and prostaglandin E1 therapy. The cumulative mortality rates in the first 20 years of life were expected to decline among cohort members born after 1978. In contrast, the mortality rates for subjects over 20 years of age increased during the 30-year study period. Mortality rates were higher for males than for females. The mortality rate among young patients with CCVM is expected to decline still further, suggesting that many if not most children with CCVM will survive to adulthood. (Circ J 2002; 66: 484–488)

Key Words: Congenital cardiovascular malformations; Mortality; Population-based mortality

Despite dramatic advances in diagnostic techniques and in surgical and medical management, congenital cardiovascular malformations (CCVM) remain a major public health problem throughout the world. In Japan, they are the leading cause of infant mortality, although overall rates of infant mortality have decreased in the past 3 decades! Mortality data are a measure of the benefits of medical and surgical therapies, but even in developed countries, mortality data on CCVM are scarce2–4 and national trends of improved prognosis are largely unknown.

In Japan, the death certification has to be registered with the Government within 7 days of demise, and must include name, sex, date of birth, date of death, age at death, place of death, and cause of death determined by the physician. The Japanese Government publishes the number and causes of death, coded according to the International Classification of Diseases (ICD), in the annual national vital statistics, but these do not include detailed analyses of age- and sex-specific CCVM mortality. Accordingly, the present study investigated these aspects and the trend for CCVM in Japan from 1968 through 1997.

Sources of Mortality Data

Our analyses of individual death records were authorized by the Japanese Government. We excluded the years before 1968 because CCVM were not specifically classified in the ICD. For 1968–1971, data were obtained from the national vital statistics and included sex, age at death and the cause of death according to the ICD code; for 1972–1997, data were obtained from individual death records registered with the Japanese Government and included the prefecture in which the patient lived, the date of birth, sex, the date of death, age at death and the cause of death according to the ICD code. In Japan, the death registration began to be computerized in 1972. Data from Okinawa prefecture were not available until 1972.

ICD Codes

During the 30-year study period, the underlying causes of death from CCVM were classified according to ICD-8 (1968–1978), ICD-9 (1979–1994) or ICD-10 (1995–1997). The codes used for CCVM were 746 and 747 in ICD-8 and 745–747 in ICD-9, but in ICD-10 CCVM were divided into 9 major codes (Q20–Q28).

During the 30-year study period, a total of 83,238 deaths from CCVM were registered with the Japanese Government and mortality data were available for all. Three hundred nineteen deaths from endocardial fibroelastosis classified as CCVM in ICD-8 were excluded because this disease was classified in a category other than CCVM in ICD-9 and ICD-10. Accordingly, a total of 82,919 deaths were analyzed. CCVM with chromosomal anomalies were not included because those cases were categorized under chromosomal anomalies.

We could not determine whether or not the patient had...
undergone surgery.

Statistics

Mortality rates from CCVM were calculated using annual population figures in Japan from 3 age groups: (1) infant, (2) 1–19 years of age, and (3) 20 years of age or more. For infant mortality, we calculated the mortality rates using the number of live births. Sex-specific rates of mortality from CCVM were also calculated.

Changes in the classification codes of the ICD during the 30-year study period made it difficult to determine long-term trends of mortality rates from specific CCVM, so we analyzed the trends of mortality from specific CCVM only from 1979 through 1994 (ICD-9). ICD-9 introduced common truncus arteriosus (745.0), transposition of great vessels (745.1), tetralogy of Fallot (745.2), common ventricle (745.3), ventricular septal defect (745.4), atrial septal defect (745.5), endocardial cushion defect (745.6), tricuspid atresia or stenosis (746.1), Ebstein anomaly (746.2), aortic valve stenosis (746.3), hypoplastic left heart syndrome (746.7) and coarctation of the aorta (747.1). ICD-9 code 745.1 (transposition of great vessels) included complete transposition of the great arteries, double outlet right ventricle and congenitally corrected transposition of the great arteries to avoid overlap with each other. The code for unspecified CCVM (ie, without a specific diagnosis) was also clarified (745.9, 746.9, 747.9).

Cumulative mortality rates were calculated in birth cohort members consisting of those born between 1972 and 1996. For each birth cohort, cumulative mortality rates were calculated as the total number of deaths by the years after birth divided by the number of live births in the calendar year in which the cohort members were born.

From 1995 to 1997 (ICD-10), infant mortality rates were compared among 6 regions in Japan to establish geographic variations. For each region, the mortality rate was calculated from the total number of infants who died of CCVM in 1995–1997 and the total number of live births 1995 through 1997.

Results

Number of Deaths From CCVM

During the 30-year study period, the number of deaths from CCVM was 82,919: 48,672 deaths (59%) occurred in the first year of life, 19,446 deaths (23%) between 1 and 19 years of age, and 14,801 deaths (18%) in adults.

Population-Based Mortality Rates

Mortality rates from CCVM declined by 64% from 3.36 per 100,000 persons in 1968 to 1.22 in 1997 (Fig 1). The highest rate was 3.56 per 100,000 persons in 1973. Since 1973, with the exceptions of 1990 and 1991, the annual rate has been lower than the year before, reaching the lowest level of 1.22 in 1997. The rates declined by 66% from 1973 to 1997.

During the 30-year study period, there were 44,192 deaths (53%) in males and 38,727 deaths (47%) in females. When the sex-specific population-based mortality was calculated, the mortality rates for males were consistently higher than those for females from 1968 through 1996 (Fig 1). In 1997, however, the rate for males was lower than for females for the first time during the 3 decades.

The infant mortality rates remained high until 1978, but declined rapidly from 127 per 100,000 live births in 1978 to 90 in 1987 and falling to 62 per 100,000 live births in 1997 (Fig 2). The mortality rates from CCVM among the population aged 1–19 years declined sharply from 3.14 per 100,000 population in 1968 to 1.30 in 1988, and finally to 1.08 in 1997. By contrast, mortality rates from CCVM among adults increased by 27% from 0.41 per 100,000.
population in 1968 to 0.52 in 1997. There was a trend to increasing mortality from 1968 to 1993, but thereafter the mortality rates have been decreasing.

Deaths in Subjects Over 60 Years of Age

During the 30-year study period, 14,801 adults over 20 years of age died of CCVM, and of these, 5,612 (38%) occurred in adults over 60 years of age. The mortality rates of adults over 60 years of age increased by 152% from 0.44 per 100,000 population in 1968 to 1.11 in 1997 and the leading CCVM in this age group was atrial septal defect.

Cumulative Mortality Rates

The cumulative mortality rates from CCVM were determined among the cohort born between 1972 and 1996. In 1972, the number of live births was 2,038,682 and of these, 2,350 died of CCVM in the first year of life. The 1972 CCVM mortality rate in the first year of life was therefore 115.3 per 100,000 live births (Fig 3). The other age-specific mortality rates in 1972 were 16.0 per 100,000 live births in the second year of life, 16.1 in the 3rd to 5th years of life, 6.7 in the 6th to 10th years of life, and 4.4 in the 11th to 20th years of life. Thus, the cumulative 1972 mortality rate in the first 20 years of life was 158.5 per 100,000 live births. Among cohort members born between 1972 and 1977, the cumulative mortality rates in the first 20 years of life remained high, but are expected to decline among cohort members born after 1978.

Specific CCVM

Mortality rates from specific CCVM are shown in Table 1 and Fig 4. The combined mortality rates from ventricular septal defect, tetralogy of Fallot and transposition of great vessels declined by 45%, from 0.82 per 100,000 population in 1979 to 0.45 in 1994. In those cases of death, most were under 20 years of age.

Mortality rates from coarctation of the aorta declined by 32%, but those from hypoplastic left heart syndrome increased by 234% and most deaths were in the first year of life.

Mortality rates from atrial septal defect were slightly increased during the study period and as noted before, most of deaths from this defect occurred in adults over 60 years. Mortality rates for other specific CCVM were 0.72 per 100,000 population in 1979 and 0.76 in 1994.

Unspecified CCVM

During the 30-year study period, 24,389 deaths (29% of total) were registered as unspecified CCVM and most of the cases were under 20 years of age. There was sustained decline in the mortality rates from 1.51 per 100,000 population in 1973 to 0.45 in 1997, and in particular, there was steep decline in the mortality rates from 1979 to 1985 (Table 1).

Sex Distribution

To determine the sex distribution in the number of deaths for each CCVM, we studied individual death records registered from 1979 to 1994 (ICD-9). The types of

<table>
<thead>
<tr>
<th>Year</th>
<th>Ventricular septal defect</th>
<th>Tetralogy of Fallot</th>
<th>Transposition of great vessels</th>
<th>Atrial septal defect</th>
<th>Coarctation of the aorta</th>
<th>Hypoplastic left heart</th>
<th>Others</th>
<th>Unspecified</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979</td>
<td>0.326</td>
<td>0.239</td>
<td>0.255</td>
<td>0.155</td>
<td>0.075</td>
<td>0.023</td>
<td>0.719</td>
<td>0.957</td>
</tr>
<tr>
<td>1980</td>
<td>0.356</td>
<td>0.233</td>
<td>0.249</td>
<td>0.173</td>
<td>0.065</td>
<td>0.034</td>
<td>0.801</td>
<td>0.821</td>
</tr>
<tr>
<td>1981</td>
<td>0.334</td>
<td>0.224</td>
<td>0.219</td>
<td>0.144</td>
<td>0.068</td>
<td>0.026</td>
<td>0.788</td>
<td>0.706</td>
</tr>
<tr>
<td>1982</td>
<td>0.314</td>
<td>0.196</td>
<td>0.226</td>
<td>0.171</td>
<td>0.084</td>
<td>0.030</td>
<td>0.796</td>
<td>0.582</td>
</tr>
<tr>
<td>1983</td>
<td>0.282</td>
<td>0.178</td>
<td>0.195</td>
<td>0.183</td>
<td>0.067</td>
<td>0.039</td>
<td>0.818</td>
<td>0.558</td>
</tr>
<tr>
<td>1984</td>
<td>0.272</td>
<td>0.179</td>
<td>0.213</td>
<td>0.177</td>
<td>0.075</td>
<td>0.044</td>
<td>0.823</td>
<td>0.505</td>
</tr>
<tr>
<td>1985</td>
<td>0.261</td>
<td>0.173</td>
<td>0.193</td>
<td>0.170</td>
<td>0.093</td>
<td>0.057</td>
<td>0.819</td>
<td>0.377</td>
</tr>
<tr>
<td>1986</td>
<td>0.236</td>
<td>0.136</td>
<td>0.173</td>
<td>0.184</td>
<td>0.074</td>
<td>0.072</td>
<td>0.801</td>
<td>0.364</td>
</tr>
<tr>
<td>1987</td>
<td>0.202</td>
<td>0.160</td>
<td>0.185</td>
<td>0.170</td>
<td>0.073</td>
<td>0.068</td>
<td>0.767</td>
<td>0.302</td>
</tr>
<tr>
<td>1988</td>
<td>0.224</td>
<td>0.122</td>
<td>0.170</td>
<td>0.174</td>
<td>0.067</td>
<td>0.065</td>
<td>0.738</td>
<td>0.320</td>
</tr>
<tr>
<td>1989</td>
<td>0.212</td>
<td>0.119</td>
<td>0.173</td>
<td>0.175</td>
<td>0.061</td>
<td>0.078</td>
<td>0.766</td>
<td>0.287</td>
</tr>
<tr>
<td>1990</td>
<td>0.200</td>
<td>0.129</td>
<td>0.168</td>
<td>0.178</td>
<td>0.077</td>
<td>0.071</td>
<td>0.784</td>
<td>0.258</td>
</tr>
<tr>
<td>1991</td>
<td>0.228</td>
<td>0.110</td>
<td>0.171</td>
<td>0.194</td>
<td>0.058</td>
<td>0.084</td>
<td>0.812</td>
<td>0.249</td>
</tr>
<tr>
<td>1992</td>
<td>0.207</td>
<td>0.116</td>
<td>0.153</td>
<td>0.173</td>
<td>0.070</td>
<td>0.087</td>
<td>0.817</td>
<td>0.237</td>
</tr>
<tr>
<td>1993</td>
<td>0.197</td>
<td>0.113</td>
<td>0.156</td>
<td>0.204</td>
<td>0.066</td>
<td>0.072</td>
<td>0.759</td>
<td>0.206</td>
</tr>
<tr>
<td>1994</td>
<td>0.215</td>
<td>0.093</td>
<td>0.140</td>
<td>0.174</td>
<td>0.051</td>
<td>0.077</td>
<td>0.762</td>
<td>0.200</td>
</tr>
</tbody>
</table>
Mortality From Heart Defects in Japan

CCVM for which death occurred predominantly in males included transposition of great vessels, tetralogy of Fallot, hypoplastic left heart syndrome, common ventricle, tricuspid atresia or stenosis, coarctation of the aorta and aortic valve stenosis (Table 2). However, the number of deaths associated with atrial septal defect was lower for males than females.

Geographic Variations

In the 3 years 1995–1997, infant mortality rates from CCVM were compared among 6 regions in Japan (Fig 5). The highest rate was in northern Japan with 76.5 per 100,000 live births compared with western Japan which had 58.8–61.3 per 100,000 live births.

Discussion

Population-Based Mortality

We have established the age- and sex-specific mortality rates from CCVM in Japan for the past 3 decades. From 1973 through 1997, there was a decreasing trend in mortality, with major advances in the management of CCVM in the 1970s, such as surgical techniques, mechanical ventilation support and the introduction of balloon atrial septostomy, contributing to the decline.

From 1979 to 1987, a sharp decline in infant mortality coincided with the advent of prostaglandin E1 and 2-dimensional echocardiography. Prostaglandin E1 was introduced in the late 1970s and widely used in the 1980s in Japan, contributing to better management of neonates with ductal-dependent critical CCVM. At the same time, 2-dimensional echocardiography was introduced and widely used in the 1980s in Japan, dramatically changing non-invasive diagnostic accuracy, especially for neonatal CCVM. The mortality rates from unspecified CCVM declined appreciably for the period from 1979 to 1985, while mortality rates from specific neonatal CCVM increased. For example, the mortality rate assigned to hypoplastic left heart syndrome rapidly increased between 1979 and 1986. Most deaths from hypoplastic left heart syndrome might have been registered as unspecified CCVM in the 1980s, resulting in an underestimation of mortality from this defect in Japan during that period.

The period from 1988 to 1993 was characterized by a lesser decline in mortality among young age groups, which reflects the learning curve for Japanese surgeons as they began to perform surgical treatment for serious heart defects in various hospitals throughout the country, including small institutes.

Cumulative Mortality Rates

We used the cumulative mortality rate of CCVM to determine the chronological changes in prognosis. Although it is best to use the cumulative death numbers divided by the number of newborns with CCVM in a specific calendar year, we could not do so because the number of newborns with CCVM was not available. Several previous studies have documented an increase over time in the identification of minor CCVM, but no change in birth prevalence of more serious defects. If the population with CCVM among newborns were constant during the observed period, the cumulative mortality rate used in this study may reflect the true mortality. The cumulative mortality rate from CCVM in the first 20 years of life was approximately 160 per 100,000 live births among cohort members born between 1972 and 1977. If 1% of live births were estimated to have CCVM, approximately 15,000–16,000 patients with CCVM per year reached adulthood in Japan from 1992 to 1997. In the USA, the population of adults with CCVM has

Table 2 Sex Distribution in the Number of Deaths From Major Congenital Cardiovascular Malformations

<table>
<thead>
<tr>
<th>Underlying cause of deaths</th>
<th>ICD-9</th>
<th>Male (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic valve stenosis</td>
<td>746.3</td>
<td>61</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>745.5</td>
<td>48</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>747.1</td>
<td>54</td>
</tr>
<tr>
<td>Common ventricle</td>
<td>745.3</td>
<td>61</td>
</tr>
<tr>
<td>Ebstein anomaly</td>
<td>746.2</td>
<td>48</td>
</tr>
<tr>
<td>Endocardial cushion defect</td>
<td>743.6</td>
<td>47</td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome</td>
<td>747.0</td>
<td>48</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>745.2</td>
<td>56</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>745.1</td>
<td>65</td>
</tr>
<tr>
<td>Transposition of the great vessels</td>
<td>746.1</td>
<td>56</td>
</tr>
<tr>
<td>Tricuspid atresia or stenosis</td>
<td>745.4</td>
<td>48</td>
</tr>
</tbody>
</table>

Fig. 4. Mortality rates per 100,000 population of the major CCVM in Japan, from 1979 through 1994 (ICD-9).

Fig. 5. Geographic variation of infant mortality rates from 1995 through 1997 in Japan. For each region, mortality rates per 100,000 live births are shown. Northern Japan comprising Hokkaido and Tohoku regions, shows the highest rate of infant mortality.
been estimated to be increasing at a rate of approximately 5% per year and it is estimated that there are now approximately 1 million such patients. A recent mortality study using individual death records in the USA also documented increased age at death from CCVM, implying that more affected patients are living to adulthood. Similarly, based upon the decline in mortality rates in this study, many if not most children with CCVM in Japan will survive to adulthood. The present study disclosed a considerable increase in the mortality rates of adults who died of CCVM. Only a small percentage of cardiologists in Japan have knowledge of or responsibility for adults with CCVM and there is a compelling need to establish health care facilities for these patients.

Geographic Variation
There was geographic variation in infant mortality among the 6 regions of Japan, with the highest rate in northern Japan where there were not any children’s hospitals during the 3 decades of this study, underscoring the need for improved health care of infants in this region.

Sex Distribution
Predominantly male mortality for CCVM was recently reported in the USA and the present study also disclosed that males were at greater risk of death. The Baltimore–Washington Infant Study showed that males predominated in abnormalities of ectomesenchymal tissue migration and in the group with left heart defects. The former abnormalities included tetralogy of Fallot, complete transposition of the great arteries, truncus arteriosus and interrupted aortic arch. The latter abnormalities included hypoplastic left heart syndrome, coarctation of the aorta and aortic valve stenosis. This sex distribution in prevalence was similar to that in mortality presented here. The sex distribution in mortality may reflect the male-to-female ratio in the prevalence of certain CCVM.

Study Limitations
Our analyses were based upon individual death records and the information is quite limited. For example, co-existing CCVM was not identified from individual death records and may result in ICD coding errors, although major abnormalities should have been described in the majority of cases. Changes in the classification codes of the ICD during the 30-year study period also made it difficult to determine long-term trends of mortality rates from specific CCVM. For this reason, we examined long-term trends of mortality only from 1979 though 1994.

The present study ignores deaths from CCVM among patients with chromosomal anomalies because these cases are categorized under chromosomal anomalies. A nationwide survey by pediatric cardiologists in Japan disclosed that associated chromosomal anomalies were found in only 5% of heart defects. This figure is lower than that seen in Western countries possibly because the prevalence of Down syndrome is lower in Japan. Nevertheless, the present study underestimated the true mortality rates from CCVM in Japan.

Conclusion
The mortality rate from CCVM in Japan has declined markedly during the past 3 decades and promises to decrease further in patients under 20 years of age, resulting in increasing numbers of children with CCVM surviving to adulthood. Sex differences in mortality may reflect male-to-female differences in the prevalence of certain CCVM in Japan. This study not only provides useful information for the trend and the age- and sex-specific mortality rates from CCVM in Japan, but serves as a basis for comparison with other countries.

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References